DETAILED ACTION

In light of the Pre-Appeal Conference request of 6/24/09, prosecution is once again opened. The finality of prosecution is now withdrawn.

Applicant's amendment and argument of 6/23/09 are entered.

Claims 9, 15, 16, 40, 41, 43-46, and 48 are amended.

Claims 1-8, 10-14, 17-39, and 47 have been cancelled during prosecution leading to the present action.

Claims 9, 15, 16, 40-46, and 48 are presently pending and considered.

Present Action Status

In accordance with the attached Interview Summary, the present Office Action is meant to supplant the Office Action of 7/8/09. The ancillary documents are not included, except for the IDS, as they have already been supplied in the Office Action of 7/8/09.

The time for reply is reset to the mailing date of the present Office Action.

Information Disclosure Statement

The Examiner has noted that the IDS of 9/23/04, while likely considered by the previous examiner, and previously considered by the present Examiner, does not appear to have been initialed, signed, and dated by the previous Examiner. Hence, to make sure this IDS is of record, the IDS is herein reconsidered, signed, initialed, and dated.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 46 be found allowable, claim 48 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 46 limits Claim 45 to administration with bupivacaine. Claim 45 depends from Claim 40 and limits it to IM administration.

Claim 48 limits Claim 44 to IM administration. Claim 44 depends from Claim 40 and limits the administrations to further comprising bupivacaine.

Hence, these claims have the same scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of the amendments, the rejections of Claims 9, 15, 16, 40-46, and 48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as necessitated by amendment, are withdrawn.

The present amendments overcome the lack of clarity of record.

Claims 15 and 43 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 43 each recite the limitation "said DNA". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of the PreAppeal Conference, it was decided to rewrite the rejections to include Art demonstrating that Macrophages are present and attracted to tissue damage sites, and make clear that these macrophages are part of the immune response and drain to local lymph nodes.

While the previous rejections are withdrawn:

Claims 9, 15-16, and 40-46, and 48 are newly rejected, under 35 U.S.C. 103(a) as being unpatentable over US PAT APP NO 2004/0063652 to Jolly; Stacey, et al. (1996) Journal of Immunology, 157: 2116-22; Kataoka, et al. (1997) J. Biol. Chem., 272(29): 18209-15; US PAT NO 5,783,567 to Hedley, et al.; Samlowski, et al. (1988) Regional Immunology, 1(1): 41-55; US PAT NO 5,763,416 to Bonadio, et al.; Roitt, et al. "Immunology" [Textbook] (1985), Published by Gower Medical Publishing, Ltd., London, England, several pages exerpted, pp. 1-1 to 1-6, 2-10 to 2-13, and 3-1 to 3-9; Yamanaka, et al. (1993) Avian Diseases, 37(2): 459-66 (ABSTRACT ONLY); Cantini, et al. (1995) Journal of Neuropathology and Experimental Neurology, 54(1): 121-28; Kadir, et al. (1992) International Journal of Clinical Pharmacology, Therapy, and Toxicology, 30(1): 374-82 (ABSTRACT ONLY); Gopalakrishnakone, et al. (1984) Toxicon: The Offical Journal of the International Society on Toxiconology, 22(1) 85-98; Beresford, et al. (1957) British Journal of Pharmacology, 12: 107-114.

Jolly teaches the use of plasmids (e.g., paragraph 0037) to effect the transformation of macrophage cells, to effect killing (e.g., paragraphs 0067-71) and for general secretion of proteins that block pathogenic interactions local to the cell (paragraph 0155), which requires secretion signals. Jolly also teaches that getting the vector to be expressed in a target lymph node is desired (e.g., paragraph 056, indicating the targeting of a particular lymph node is a desireable feature). Lastly, Jolly teaches bupivacaine as an additive to enhance transfection (paragraph 0365).

Still further, with regard to the possibility that Jolly is randomly teaching the use of plasmids and it is not enabled, Stacey teaches that plasmids are taken up by macrophages and

transgenes are expressed (e.g., Figure 6). Hence, the Artisan knows specifically that macrophages will pick up plasmids and express the transgenes therein.

Kataoka teaches the human CD156 gene, and its promoter sequence as specific for macrophage expression, as well as the structure of such promoters (p. 18215).

Hedley teaches the transformation of macrophages of the draining lymph nodes by subcutaneous injection (e.g., col. 8, paragraph 3), and Samlowski teaches that macrophages were known to drain to the lymph nodes local to the site of injection (e.g., ABSTRACT), hence, macrophages drain locally and not distantly.

Bonadio teaches that the SV40 polyA signal is a standard signal for termination of transcripts (e.g., EXAMPLE IX).

Roitt provides a very detailed understanding of the flow of monocytes to sites of injury and to the lymph nodes to be recirculated. Specifically, it is noted that page 3-8 provides Figure 3.24 which demonstrates that lymphocytes travel through the peripherial tissues, to lymph nodes, and then into several possible locations, one of which is to return to the peripherial tissues. Further, it is noted that page 1-4 demonstrates that macrophages flow specifically out of the circulatory system (the blood) into damaged tissues (last paragraph). Further, it is noted that monocytes can migrate out of the blood to the site of injury and differentiate into more macrophages (p. 1-3, paragraph bridging columns). Still further, it is noted that it is well known that the whole body contains a lymph node network, to circulate the various lymphocytes back to the thoracic duct, and nodes are known to be located throughout, as well as particularly at branches of the lymphatic vessels (p. 3-4). Hence, the Artisan knows that the macrophages will

drain to the lymph nodes. Still further, Roitt teaches that the antigens are processed in the lymph nodes for immune responses (e.g., pp. 3-4 to 3-7).

Moreover, as further evidence that macrophages are found as a response to muscle tissue damage, Yamanaka, Cantini, Kadir, Gopalakrishnakone, and Beresford each demonstrate that as far back as 1957, it was well known that macrophages respond to tissue damage in muscle by migrating to the damage site (See the ABSTRACTs of each article).

From the confluence of this, it is clear that Jolly teaches transfection of macrophages *in vivo* with plasmids, Hedley and Samlowski teaches that transformation of the macrophages will lead to transfected macrophages in the draining lymph nodes, Roitt demonstrates that the Artisan understands the circulation of Macrophages and that they circulate through all tissues, Yamanaka, Cantini, Kadir, Gopalakrishnakone, and Beresford demonstrate that the macrophages are specifically attracted to the site of muscle tissue damage, and Kataoka and Bonadio teach the required signals for expression of a gene in macrophages.

Further, when injecting substances, it is standard in the Art to administer substances which numb the area to avoid hurting the subject. One such substance which was well known in the Art is Bupivacaine (http://www.drugdigest.org/DD/DVH/Uses/0,3915,7903%7CBupivacaine%2BHCL,00.html). Such if further noted, in Jolly, to be a compound to use for IM injection and will enhance free DNA expression, which is, absent reason to believe otherwise, occuring through enhancing transfection (See portion discussing Jolly, ABOVE). Hence, the further administration of Bupivacaine was well known in the Art for such use, and as such the further utilization of Bupivacaine would be obvious.

Therefore, at the time of invention, the method would have been obvious. The Artisan would be motivated to choose a site local to the lymph node target, which will be intramuscular, depending on which lymph nodes are being targeted (it is well known in the Art that lymph nodes are located throughout the body and near muscle) because the macrophages were known to drain to local lymph nodes. One such motivation is to produce proteins delivered to the lymph node, which provides for more immunologic processing. Still further, the Artisan would inject the plasmid by IM injection in order to deliver it to a lymph node local to the muscle injection site, via the understood attraction of macrophages like in Hedley and Samlowski, but to muscle, as is shown in Roitt's understanding of migration of macrophages, and the teachings of Yamanaka, Cantini, Kadir, Gopalakrishnakone, and Beresford, which show that macrophages migrate to the site of damage in muscle tissue. Still further, the administration of Bupivacaine to a subject during or prior to injection of the vector would be motivated in order to avoid pain in the subject due to administration. Moreover, the Artisan would have expected success, as the transformation of macrophages was already known and the draining of such macrophages to lymph nodes was well known in the Art. In addition, the obtained result would necessarily be obtained as the macrophage is secreting the protein.

Lastly, it should be noted that the references for IM administration are not required for Claims 40, 41, 42, 43, and 44, as these claims encompass at least subcutaneous injection.

Response to Argument – obviousness

Applicant's argument of 6/23/09 has been fully considered but is not found persuasive.

Applicant argues that none of the references discuss identifying a lymph node as a target for delivery of a protein and locating a site local to the lymph node (p. 7, paragraph 3).

Such is not persuasive. Jolly teaches targeting lymph nodes. Moreover, Roitt teaches the circulation of the macrophages through the circulatory system, to sites of injury, and draining through the lymph node, as also emphasized by Yamanaka, Cantini, Kadir, Gopalakrishnakone, and Beresford demonstrating that the macrophages also go to the site of injury in the muscle. Jolly teaches that the proteins are provided to to effect killing (e.g., paragraphs 0067-71) and for general secretion of proteins that block pathogenic interactions local to the cell (paragraph 0155), which requires secretion signals. Still further, it is obvious to get proteins into the lymph nodes through this method, as Jolly teaches targeting of lymph nodes (e.g., paragraph 056). Still further, Jolly teaches the expression of proteins for enhancing immunity, which is also effected in the lymphatic system (Roitt).

Applicant argues that the references do not teach that DNA administration leads to macrophages taking up the DNA and the macrophage drains to the lymph node (p. 7, paragraph 3).

The rejection has been changed to demonstrate that the Artisan understood specifically that macrophages take up DNA, and that macrophages drain to the lymph nodes locally, and finally, that macrophages migrate to the site of tissue damage in muscle, so they can pick up the DNA.

Applicant argues that Jolly does not disclose how to administer the vector to a macrophage and that Jolly fails to disclose the step of identifying the lymph node and delivery by administering a DNA to a site that is local to the lymph node (p. 7, paragraph 4).

Such is not persuasive. The choice of a lymph node may be as broad as "a lymph node into which muscle attracted macrophages drain", and hence, all lymph nodes near the muscle are

identified. Second, the choice of delivery to a specific lymph node would be that choice which is inherent in the method of choosing to deliver the protein to a specific lymph node. Because the Artisan knows the lymphatic system, and that macrophages which migrate to tissues will then migrate to lymph nodes local to the site, the choice is obvious to the methods being performed. If the Artisan wishes to co-localize responses in the lymphatic system to a lymph node which is being studied, this method allows the Artisan to choose the lymph node which will be utilized. With regard to administration to macrophages, the macrophages are attracted to the damage, as shown, and the plasmids are taken up and expressed by the macrophages, as demonstrated above.

Applicant argues that Hedley teaches away from the use of free DNA and intramuscular delivery because it discusses microparticles (p. 7, last paragraph).

Such is not persuasive. Teaching away means that it disparages the other. In teaching that microparticles may be used, it does not say that plasmids may not be used. Further, as evidenced above, the scope of free DNA, given its broadest reasonable interpretation is broader than plasmids.

Applicant argues that Hedley is limited to subcutaneous injection (p. 8, paragraph 1).

Such is not persuasive. Hedley is simply used to emphasize the teachings of Roitt, and further, the other new art demonstrates that macrophages also go to muscle damage sites.

Applicant argues that Hedley teaches IM injection of microparticles to target dendritic cells and not to macrophages (p. 8, paragraph 1, citing Column 8, lines 22-24).

Such is not persuasive. The cited portion fails to discuss IM injection at all, and is a description of CTL response in subcutaneously-injected mice. If Applicant is arguing that IM is so distinct from subcutaneous administration, it would appear that the argument is also distinct

from the present rejection. However, it is argued that a macrophage is a macrophage, and given the other teachings that the macrophages also migrate to injury sites in muscle, just like subcutaneous injury, the Artisan would have no reason to doubt that these macrophages will similarly uptake the vector. Simply put, the stating that "one can target, via subcutaneous injection, take up by the phagocytic cells of the draining lymph nodes" does not mean that one cannot target take up by the phagocytic cells of the draining lymph nodes. Applicant's implied argument appears to be that no one would choose a lymph node near the muscle, because the Artisan did not know if macrophages responded to muscle damage, and if they drained to lymph. Hence, if such were the case, the claimed method would appear allowable, as Applicant would have, in such case, produced a novel and non-obvious method, however, as is shown, this is known, and therefore, the alternative use of muscle injection would be obvious.

Applicant argues that Hedley teaches that the particles of Hedley are superior to naked DNA, and hence, it teaches away from the use of plasmids (p. 8, paragraph 2). Still further, it should be noted that other references show the same for sub-subcutaneous injection, and Applicant has not amended to remove subcutaneous injection from Claims 40-44. Clearly subcutaneous injection is had, e.g., by Hedley and Samlowski. If Applicant is serious, such would appear to require addressing.

Such is not persuasive. Hedley teaches an optimum vector for his processes, and this does not mean that other vectors, like plasmids, would not work. Just because Hedley found conditions to provide his particles in a higher effectiveness than plasmid, does not mean that plasmids are ineffective. Still further, Hedley is a free DNA, because, e.g., it is free of being enacapsulated. Clearly, Applicant's discussion of free DNA in the specification (in the

Examples) is limited to encapsulation, as everything about the first paragraph on page 39 discusses the availability of DNA directly to the macrophage, and a hypothetical DNA receptor on the surface of macrophages. Applicant's discussion does not, however, mean that the DNA is required to be free of everything. It is not required to be free of histones or other proteins that complex the DNA, and hence, DNA complexes are surely encompassed by claims. Hence, e.g., Hedley's disclosure is also encompassed. Still further, the core of the rejection was directed to the plasmid, and hence, Hedley's teaching on the vector is irrelevant, and as noted above, Hedley does not teach that plasmids won't work, and hence, it does not "teach away".

Applicant argues Jolly does not disclose the elements of the claims, and the other references do not make up for the differences, and hence, there is no prima facie case of obviousness (p. 8, penultimate paragraph).

Such is not persuasive. The added art makes up for the deficiencies. The Examiner has attempted to fill in the water is wet references required to state the obvious.

Applicant argues that an unexpected result of the invention is that no one would expect that IM injection would lead to delivery of a protein to a lymph node (pp. 8-9, paragraph bridging).

Such is not persuasive. As is hopefully covered in Roitt, processing occurs in the lymph. It has very long been known that foreign particles are delivered to the lymph nodes when they invade a tissue. It is part of the normal immune response.

Applicant argues that no one would expect free DNA to deliver a protein to a lymph node (p. 9, paragraph 2).

Such is not persuasive. It has long been known that proteins expressed from transfected cells at a damage site are delivered to the lymph nodes local to the site. With regard to free DNA, any vector which transforms a cell would yield expression of the proteins encoded, as long as it can be expressed by the species of cell. In specific, it is shown in the new art that macrophages take up and express foreign transgenes from plasmids. Still further, Roitt, on page 3-5 demonstrates that the foreign antigens are well known to be delivered to the lymph node.

Applicant argues articulated reasoning. The Examiner has re-articulated the reasoning, with increased art cited, above.

CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Primary Examiner of Art Unit 1633